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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/249,529	02/12/1999	JAMES D. MARKS	02307E-08521	1036

7590 09/23/2002

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EXAMINER
PONNALURI, PADMASHRI

ART UNIT	PAPER NUMBER
1627	

DATE MAILED: 09/23/2002 25

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/249,529	Marks et al
Examiner	**Art Unit**
Padmashri Ponnaluri	1627

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *May 13, 2002* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-17 and 51-57* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-17 and 51-57* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. A request for continued examination under 37 CAR 1.114, including the fee set forth in 37 CAR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CAR 1.114, and the fee set forth in 37 CAR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CAR 1.114. Applicant's submission filed on 5/13/02 has been entered.

2. The amendment A, filed on 5/13/02 has been fully considered and entered into the application.

3. Claims 18-50 have been canceled by the amendment A, filed on 5/13/02.

4. New claims 51-57 have been added by the amendment A.

5. Claims 1-17 and 51-57 are currently pending and are being examined in this application.

6. This application has been filed with informal drawings. Formal drawings will be required when the application is allowed.

Applicant is invited to notice that boxes 5 and 12 were checked by the draftsman. If applicants renumber the figures, applicant is encouraged to amend the specification so that the description of renumbered figures corresponds to the renumbered figures.

7. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claim 11 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is new matter rejection.

The limitation 'wherein step (ii) is performed at about 4^0 C' claimed in claim 11 has no clear support in the specification and the claims as originally filed. The step (ii) in claim 1 recites removing and eliminating members of said library that are bound to the exterior surface of said target cells with a strong wash. The specification does not disclose the temperature at the wash is conducted to remove the unbound phage. The subject matter claimed in claim 11 changes the scope of the invention as originally disclosed in the specification.

If applicants disagree, applicant should present a detailed analysis as to why the claimed subject matter has clear support in the specification.

10. Claim 52 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is new matter rejection.

The limitation 'live cells of substractive cell line' claimed in claim 52 has no clear support in the specification and the claims as originally filed.. The specification does not disclose

that eh substractive cell line comprises live cells. The subject matter claimed in claim 52 broadens the scope of the invention as originally disclosed in the specification.

If applicants disagree, applicant should present a detailed analysis as to why the claimed subject matter has clear support in the specification.

11. Claims 55 and 56 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is new matter rejection.

The limitation 'removing comprises contacting the target cells with **trypsin**' claimed in claims 55 and 56 has no clear support in the specification and the claims as originally filed. The step (ii) in claim 1 recites removing and eliminating members of said library that are bound to the exterior surface of said target cells with a strong wash. The specification discloses that the unbound phage or weakly bound phage are removed using "**low pH glycine**" (i.e., see page 40, line 17 or page 41, lines 16-17). The specification does not disclose the 'Trypsin' is used to wash the weakly bound phage. The subject matter claimed in claims 55-56 changes the scope of the invention as originally disclosed in the specification.

If applicants disagree, applicant should present a detailed analysis as to why the claimed subject matter has clear support in the specification.

12.The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13.The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 1-17 and 51-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite by reciting 'strong wash', which is a relative term. The specification does not define what the strong wash is. Applicants are requested to define the wash by the properties or the name of the reagents used in the wash.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the claim does not recite how the internalized members of the library are identified. Does the internalization of the polypeptide into the target cell is indicated by any signal or marker. Applicants are requested to amend the claims to include all the method steps.

Claim 8 recites the limitation "said cells of a substractive cell line". There is insufficient antecedent basis for this limitation in the claim.

Claim 10 is vague and indefinite by reciting that 'step (ii) is performed at a temperature lower than step (iv)'. Applicants are requested to amend the claim since claim does not recite step (iv).

Claim 16 recites the limitation "said cells of a substractive cell line". There is insufficient antecedent basis for this limitation in the claim.

Claim 17 recites the limitation "said cells of a substractive cell line". There is insufficient antecedent basis for this limitation in the claim.

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

16. Claims 1-7, 12-15, and 53 are rejected under 35 U.S.C. 102(b) as being anticipated by Barry et al (Nature Medicine, vol. 2, no. 3, March 1996, pages 299-305).

Barry et al teach a method to generate cell targeting ligands using peptide presenting phage libraries to select peptides that bind and enter several different cell types. The reference teaches peptide presenting phage libraries (random amino acids) fused to the amino terminus of the pIII protein. The reference teaches a method to identify the cells which bind to the phage and

the selected phage or peptide sequence is determined. The reference teaches that the peptide presenting phage are useful as gene delivery vehicles. The reference teaches that the phage bearing the peptide and a luciferase (detectable product or selectable product of the instant claims 12-14) plasmid is used to mediate transfection of fibroblast cells (refers to target cells of the instant claims), and the bacteriophage is useful in gene therapy. Barry et al teach that the phage were incubated with cells for 1 hour at 4^0 C or 37^0 C, and the cells were washed 6 times with cold PBS-BSA and then the cells were incubated with 2 ml of 0.1 M HCL pH 2.2 by Glycine (refers to the strong wash of the instant claims). The cells were lysed (see page 304, right column). The reference clearly anticipates the claimed invention.

17. Claims 1-7, and 12-15 are rejected under 35 U.S.C. 102(e) as being anticipated by Larocca et al (US Patent 6,054,312).

Larocca et al teach receptor mediated gene delivery using bacteriophage vectors. The reference teaches that a library of random peptides is engineered into gene VIII protein of a phage vector that has ligand fused to gene III and that carries a detectable (e.g., GFP) or selectable marker (drug resistance) (see column 8). Mammalian cells are infected with the library and the cells selected by detection of the marker (see column 8). The reference teaches that multiple rounds of selection may be performed to reduce the complexity of the recovered peptide encoding genes. The reference teaches that the antibodies such as antibodies to FGF receptors, VEGF receptors, urokinase receptor, E- and P-selectins, PDGF receptor.... are used for internalization (refers to instant claims 2, 3). The reference teaches fusion proteins comprise gene

encoding all or a receptor-binding polypeptide portion of a ligand (or mAb, Fab) genetically fused or linked to coat protein encoding gene of a bacteriophage particle. The reference teaches that the nucleotide sequences encoding the ligand-phase fusions may be further modified via insertion of a mammalian reporter gene (refers to the instant claims 12), in order to further verify binding and internalization, as well expression of the nucleic acid. The reference teaches that the reporter gene is EGFP (refers to instant claim 13), which is translated into green fluorescent protein (GFP) when gene delivery and expression occur and other reporter genes include beta-galactosidase, luciferase..... (refers to instant claim 14). The reference teaches that the phage vectors carrying a ligand can be used to internalize into the various different cell types including tumor cells. Thus, the reference clearly anticipates the claimed invention.

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CAR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

19. Claims 1-17, 51-54 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barry et al (Nature Medicine, vol. 2, no. 3, March 1996, pages 299-305) in view of either Ewjik et al (Proc. Natl. Acad. Sci. USA, vol. 94, pp 3903-3908, April 1997) or Stausbol-Gron et al (FEBS Letters, vol. 39., pages 71-75, 1996).

Barry et al teach a method to generate cell targeting ligands using peptide presenting phage libraries to select peptides that bind and enter several different cell types. The reference teaches peptide presenting phage libraries (random amino acids) fused to the amino terminus of the pIII protein. The reference teaches a method to identify the cells which bind to the phage and the selected phage or peptide sequence is determined. The reference teaches that the peptide presenting phage are useful as gene delivery vehicles. The reference teaches that the phage bearing the peptide and a luciferase (detectable product or selectable product of the instant claims) plasmid (refers to instant claim 24) is used to mediate transfection of fibroblast cells, and the bacteriophage is useful in gene therapy. Barry et al teach that the phage were incubated with cells for 1 hour at 4^0 C or 37^0 C, and the cells were washed 6 times with cold PBS-BSA and then the cells were incubated with 2 ml of 0.1 M HCL pH 2.2 by Glycine (refers to the strong wash of the instant claims). The cells were lysed (see page 304, right column).

The claimed invention differs from the prior art teachings by reciting the use of subtractive cell line. Barry et al teach method to generate cell targeting ligands and a method to identify the cells that bind to phage. Barry et al do not teach the use of subtractive strategy to eliminate non specific binding of phage members to target cells. However, either Ewijk et al or Stausbol-Gron et al teach phage display subtraction method.

Stausbol-Gron et al teach phage display subtraction method with potential for analysis of differential gene expression. The reference teaches that a competitive bio-panning procedure was developed and tested on two model systems using a phagemid library of single chain Fv antibody fragments. The reference teaches that the phage library was incubated with targets and competitive proteins at 4^0 C, and the bound phage was eluted and propagated at 37^0 C. The reference teaches that the subtractive panning strategy is fast and easy way to identify research reagents directed against biomarkers of cellular extracts or biological fluids. The reference teaches that the subtractive strategy is valuable in attempts to identify antibodies against known or unknown antigens in a given population of cells.

Ewijk et al teach subtractive isolation of phage-displayed single-chain antibodies to thymic stromal cells by intact thymic fragments. The reference teaches the use of phage antibody display technology with specific aim to isolate thymic stromal cell specific single chain antibodies from a phage library. A subtractive approach using intact, mildly fixed thymic fragments as target tissue and thymocytes and spleen cells used to remove undesired specificities of the phage antibody library. The reference teaches that the phage library was incubated with

thymocytes and spleen cells; to this target cells (thymic fragments) have added and incubated at 4^0 C. The following day the supernatant was removed and the target cells were washed to remove nonspecifically adhered phages. The specifically bound phage and thymic fragments were cultured at 37^0 C, and the specific phage was identified. The reference teaches that the subtractive isolation using thymocytes and splenocytes as adsorber cells, and using thymic cells as target cells, they were able to isolate monoclonal phage antibodies reactive with thymic stromal cell types, while monoclonal phage antibodies to lymphoid cells were not detected.

Thus, it would have been obvious to a person of ordinary skill in the art to use the subtractive isolation of phage displayed single chain antibodies to remove nonspecifically bound members of phage library as taught by Ewijk et al or the subtraction method taught by Stausbol-Gron et al with the method of Barry et al to identify phage display members which transfer (or internalize) the specific gene to target cells, because Barry et al teach individual phage bearing the specific peptide can be isolated from the library using luciferase, the phage bearing the specific peptide is useful in gene therapy, Ewijk et al teach that the phage display technology can be applied to isolate scFvs directed to specific cell types in presence of other kinds of cells and Stausbol-Gron et al teach that the subtractive panning strategy is fast and easy way to identify research reagents directed against biomarkers of cellular extracts or biological fluids and it is valuable in attempts to identify antibodies against known or unknown antigens in a given population of cells. The person of ordinary skill in the art would have been motivated to use the

subtractive strategy in the method of gene transfer taught by Barry et al with the expectation of eliminating non specific binding of members of phage display library with target cells.

20. Claims 1-17, 51-54 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 6,054,312 (Larocca et al) (filing date 29 August, 1997) in view of either Ewjik et al (Proc. Natl. Acad. Sci. USA, vol. 94, pp 3903-3908, April 1997) or Stausbol-Gron et al (FEBS Letters, vol. 39., pages 71-75, 1996).

Larocca et al teach receptor mediated gene delivery using bacteriophage vectors. The reference teaches that a library of random peptides is engineered into gene VII protein of a phage vector that has ligand fused to gene III and that carries a detectable (e.g., GFP) or selectable marker. Mammalian cells are infected with the library and the cells selected by detection of the marker. The cells that have the highest expression have been recovered, and the peptide genes are encoded into the phage vectors. The reference teaches fusion proteins comprise gene encoding all or a receptor-binding polypeptide portion of a ligand (or mAb, Fab) genetically fused or linked to coat protein encoding gene of a bacteriophage particle. The reference teaches that the nucleotide sequences encoding the ligand-phase fusions may be further modified via insertion of a mammalian reporter gene, in order to further verify binding and internalization, as well expression of the nucleic acid. The reference teaches that the reporter gene is EGFP, which is translated into green fluorescent protein (GFP) when gene delivery and expression occur.

The claimed invention differs from the prior art teachings by reciting method of removal of non specific binding of phage display library members to target cells by using subtractive

strategy. Larocca et al teach receptor mediated gene delivery using bacteriophage vectors. Larocca et al do not teach the removal of non specific binding phage using subtractive strategy. However, either Ewijk et al or Stausbol-Gron et al teach phage display subtraction method. Ewijk et al teach subtractive isolation of phage-displayed single-chain antibodies to thymic stromal cells by intact thymic fragments. The reference teaches the use of phage antibody display technology with specific aim to isolate thymic stromal cell specific single chain antibodies from a phage library. A subtractive approach using intact, mildly fixed thymic fragments as target tissue and thymocytes and spleen cells used to remove undesired specificities of the phage antibody library. The reference teaches that the phage library was incubated with thymocytes and spleen cells; to this target cells (thymic fragments) have added and incubated at 4^0 C. The following day the supernatant was removed and the target cells were washed to remove nonspecifically adhered phages. The specifically bound phage and thymic fragments were cultured at 37^0 C, and the specific phage was identified. The reference teaches that the subtractive isolation using thymocytes and splenocytes as adsorber cells, and using thymic cells as target cells, they were able to isolate monoclonal phage antibodies reactive with thymic stromal cell types, while monoclonal phage antibodies to lymphoid cells were not detected.

Stausbol-Gron et al teach phage display subtraction method with potential for analysis of differential gene expression. The reference teaches that a competitive bio-panning procedure was developed and tested on two model systems using a phagemid library of single chain Fv antibody fragments. The reference teaches that the phage library was incubated with targets and

competitive proteins at 4^0 C, and the bound phage was eluted and propagated at 37^0 C. The reference teaches that the subtractive panning strategy is fast and easy way to identify research reagents directed against biomarkers of cellular extracts or biological fluids. The reference teaches that the subtractive strategy is valuable in attempts to identify antibodies against known or unknown antigens in a given population of cells. Thus, it would have been obvious to a person of ordinary skill in the art to use the subtractive isolation of phage displayed single chain antibodies to remove nonspecifically bound members of phage library as taught by Ewijk et al or the subtraction method taught by Stausbol-Gron et al with the method of Larocca et al to identify phage display members which transfer (or internalize) the specific gene to target cells, because Larocca teach individual phage which express the peptide of interest can be isolated from the library, and targeted gene transfer technique has number of uses in research, in therapy and in diagnostics, Ewijk et al teach that the phage display technology can be applied to isolate scFvs directed to specific cell types in presence of other kinds of cells and Stausbol-Gron et al teach that the subtractive panning strategy is fast and easy way to identify research reagents directed against biomarkers of cellular extracts or biological fluids and it is valuable in attempts to identify antibodies against known or unknown antigens in a given population of cells.

21. Applicant's arguments filed on 5/13/02, regarding the art rejections of record have been fully considered but are not persuasive. Applicants arguments have been based on that the claimed invention differs from the prior art teachings by reciting the use of 'live substractive cells' and the use of a 'Low pH Wash to remove the unbound phage'. Applicants arguments have

been fully considered but are not persuasive. These arguments are moot in regard to the independent claim 1, since the amended claim 1 does not recite any of these limitations. And applicants have not shown support in the specification for the new limitations. Applicants arguments are moot in view of new grounds of rejections.

22. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to P. Ponnaluri whose telephone number is (703) 305-3884. The examiner is on ***Increased Flex Schedule*** and can normally be reached on Monday to Friday from 7.00 AM to 3.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on (703) 306-3217. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

P. Ponnaluri
Patent Examiner
Technology Center 1600
Art Unit 1627
19 September 2002

PADMASHRI PONNALURI
PRIMARY EXAMINER